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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,803	01/14/2004	James McSwiggen	MBHB03-465-C (400.142)	5421

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EXAMINER	
BOWMAN, AMY HUDSON	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
10/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,803	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-20 and 33-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-20 and 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/16/07, 10/4/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 8/16/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 12/21/2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 18-20 and 33-38 are pending in the application.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's arguments and/or amendments filed 8/16/07, with respect to the rejection(s) of claim(s) under 35 USC 112, 2nd paragraph have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made as explained below.

Priority

The instant claims are accorded the priority date of 2/20/2002, which is the filing date of application 60/358,580, because application PCT/US03/05346 and application 60/358,580 each teach each of the limitations of claims 18-20 and 33-38.

Response to Arguments--Claim Rejections - 35 USC § 103

Claims 18-20 and 33-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al. (The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888), in view of Matulic-Adamic et al. (US 5,998,203), Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000), and Crooke (US 5,898,031), for the reasons of record set forth in the office action mailed on 12/21/06 and the advisory actions mailed on 3/27/07 and 5/1/07.

Applicant asserts that at the 2002 priority date of the present claims, it was not believed that the chemical modifications would be necessary for double stranded constructs. Applicant asserts that it was not known or predictable given how little was understood regarding the mechanism of siRNA, whether modifications from the antisense and ribozyme arts would impart desired properties without interfering with the ability of the double stranded constructs to induce RNAi.

Contrary to applicant's assertions, Elbashir et al. and Parrish et al. are evidence that it was known at the time of the instant priority date to incorporate known chemical modifications that have enhanced the activity of other sequence specific inhibitory nucleic acid molecules, such as antisense oligonucleotides or ribozymes, into siRNA

molecules or dsRNA molecules, respectively. Parrish teaches that the 2'-deoxy-2'-fluoro modifications incorporated into the long dsRNA produces unc-22 interference and furthermore described the interference as strong (+++, see figure 5). The instant chemical modifications were known in the art to benefit in the delivery of inhibitory nucleic acid molecules and it was known that each of antisense oligonucleotides, ribozymes or siRNA duplexes, desire enhanced delivery to cells.

Since Crooke teaches effectively walking modifications across antisense oligonucleotides to optimize the location of the modifications and activity of the oligonucleotide and Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach successfully synthesizing modified double stranded nucleic acid molecules, one would reasonably expect for each of the modifications to benefit the double stranded nucleic acid molecules of Elbashir et al. as well. Furthermore, the long chemically modified dsRNA taught by Parrish et al. further demonstrate that extensively modified dsRNA molecules result in interference activity. Since Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach extensive modification of double stranded nucleic acid molecules and Crooke teaches experimentally determining optimal locations and levels of modification of antisense oligonucleotides, incorporating each of the modifications in the double stranded nucleic acid molecules of Elbashir et al. is considered within the realm of routine optimization.

Although applicant asserts that it was not known or predictable given how little was understood regarding the mechanism of siRNA, whether modifications from the antisense and ribozyme arts would impart desired properties without interfering with the

ability of the double stranded constructs to induce RNAi, it would have certainly been obvious to incorporate the modifications into the siRNA molecules of Elbashir et al. in order to determine the optimal configurations and modifications, particularly in view of the fact that Elbashir did test some of the modifications at some percentages.

It would have been prima facie obvious to perform routine optimization to determine which of the known modifications or combinations of modifications are optimal. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of the specific modifications used were other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Applicant asserts that Elbashir reported marginal success, which would not have informed the particular chemical modification patterns recited in the present claims, finding that the ability to induce RNAi was retained only when 2 or 4 ribonucleotides at the siRNA ends were replaced with deoxy ribonucleotides and that replacement of all ribonucleotides in one or both strands with deoxy ribonucleotides or 2'-O-methyl substituted nucleotides abolished activity. It is noted that the instant broad claim 18 only requires a terminal cap moiety at the 5'- and 3'-ends of the first strand, and an optional 3'-end terminal cap on the second strand. The dependent claims further

require one or more of a type of chemical modification. This level of modification would certainly be considered obvious in view of the successful modifications of Elbashir et al. and Parrish et al.

The instant genus is huge, encompassing nucleic acid molecules that are modified with a multitude of possible chemical modifications or combinations of chemical modifications that were known in the antisense and ribozyme art. It is considered that there would be some configuration of the chemical modifications that were known in the art to benefit other nucleic acid molecules such as antisense oligonucleotides or ribozymes that would retain RNAi activity when incorporated into nucleic acid molecules. Due to the breadth of the instant claims, the teachings of Elbashir et al. are considered to be motivation with regards to extensively modifying nucleic acid duplexes to optimize the activity therein. Although Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity, there are no instant claims that are identical in scope to the teachings of Elbashir et al. Therefore, within the huge genus of molecules that are being instantly claimed, the teachings of Elbashir et al. are considered to offer motivation to test various types of known chemical modifications at different percentages in order to optimize the activity of the molecule. Elbashir et al. also teaches successful inhibition with chemically modified siRNA molecules and are silent as to chemically modified siRNA molecules with any other types of modifications or that are modified at over 19% of the positions, but less than 100% of the positions.

Furthermore, it is noted that ribozymes are sequence specific inhibitory nucleic acid molecules that rely on activity with a complex secondary structure. Although ribozymes are faced with the complexity of structure, it is well known in the nucleic acid art to incorporate extensive levels of chemical modification to enhance the activity of the molecule and to specifically incorporate each of the instantly recited modifications, as evidenced by Matulic-Adamic et al.

The instant specification discloses a multitude of oligonucleotide and ribozyme art regarding chemical modifications and teaches that "Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis, and are incorporated by reference herein. In view of these teachings, similar modifications can be used as described herein to modify the siNA nucleic acid molecules of the instant invention so long as the ability of siNA to promote RNAi in cells is not significantly inhibited." (see page 112).

It is acknowledged that the specification is not to be relied upon for a source of motivation and that is not considered to be the instant case. The specification is merely being relied upon to distinguish that applicant recognized that double stranded nucleic acid modification is dependent upon the state of the art of oligonucleotides and ribozymes and that previously beneficial chemical modifications would be used with double stranded nucleic acid molecules as well.

Since Elbashir et al. (EMBO), Matulic-Adamic et al., and Parrish et al. teach modified double stranded nucleic acid molecules that inhibit target gene expression,

and Crooke teaches gapmer oligonucleotide chemistry to improve pharmacokinetic properties of the oligonucleotide, one would have been motivated to synthesize duplexes, as taught by Elbashir et al., with each of the instantly recited modifications, as taught by Elbashir et al., Matulic-Adamic et al., and Parrish et al. in order to optimize the activity of the molecule, as taught by Crooke.

Additionally, antisense oligonucleotides, ribozymes, and dsRNAs are each commonly used for sequence-specific mRNA knockdown and each of these encounters the same problems for effective application. Therefore, one would have been motivated to utilize the same modifications and techniques that have been utilized to overcome these problems with antisense oligonucleotides or ribozymes with siRNAs to add the same benefits to RNAi technology.

Finally, one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to antisense oligonucleotides, ribozymes or siRNA duplexes, as evidenced by Elbashir et al., Matulic-Adamic et al., Parrish et al. and Crooke, wherein each of the molecules face the same challenges, and each of which can be improved with modifications. Since Crooke teaches effectively walking modifications across antisense oligonucleotides to optimize the location of the modifications and activity of the oligonucleotide and Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach successfully synthesizing modified double stranded nucleic acid molecules, one would reasonably expect for each of the modifications to benefit the double stranded nucleic acid molecules of Elbashir et al. as well. Furthermore, the long chemically modified

dsRNA taught by Parrish et al. further demonstrate that extensively modified dsRNA molecules result in activity. Since Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach extensive modification of double stranded nucleic acid molecules and Crooke teaches experimentally determining optimal locations and levels of modification of antisense oligonucleotides, incorporating each of the modifications in the double stranded nucleic acid molecules of Elbashir et al. is considered within the realm of routine optimization.

It is noted that Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity. However, regardless of the results of these specific modifications at 100% of the positions of one or both strands, Elbashir et al. did modify duplexes and published data regarding successful inhibition with some duplexes and unsuccessful inhibition with others, supporting that testing of such known chemical modifications is routine in the art. The results of Elbashir et al. are considered to offer motivation to incorporate chemical modifications at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

New Objections/ Rejections

Claim Objections

Claim 36 is objected to because of the following informalities: Claim 36 does not end with a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-20 and 33-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 recites the limitations "said 3'-end terminal cap moieties" and "said 5'-end cap moiety". However, there is insufficient antecedent basis for these limitations in the claim. Recitation of "wherein the 3'-end terminal cap moieties" and "the terminal cap moiety at the 5'-end", for example, would obviate this rejection.

Claims 19, 20 and 33-38 are rejected because they depend from claim 18.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 18-20 and 33-38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 15-18, 32, 36-40, 42-44, and 46-51 of copending Application No. 10/667,271. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to chemically modified double stranded nucleic acid molecules with overlapping structural characteristics and modifications. The instant molecules are not designed to be targeted to any specific target RNA sequence and are therefore anticipated by the claims of application '271, that recite molecules with overlapping structural characteristics that are targeted to HCV RNA.

Application '271 recites double stranded nucleic acid molecules directed to HCV RNA, wherein the molecules comprise a sense and an antisense strand, wherein each strand is 18 to 27 nucleotides in length. Application '271 recites 2'-deoxy, 2'-deoxy-2'-fluoro, and 2'-O-methyl modifications at varying amounts in one or both strands, as well as terminal cap moieties including inverted deoxy abasic moieties and LNA nucleotides.

Application '271 recites a composition comprising the nucleic acid molecule in a pharmaceutically acceptable carrier or diluent. Therefore, the instant claims are obvious in view of the claims of application '271.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 18-20 and 33-38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 15-18, 32, 36-40, 42-44, and 46-51 of copending Application No. 10/669,841. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to chemically modified double stranded nucleic acid molecules with overlapping structural characteristics and modifications. The instant molecules are not designed to be targeted to any specific target RNA sequence and are therefore anticipated by the claims of application '841, that recite molecules with overlapping structural characteristics that are targeted to HBV RNA.

Application '841 recites double stranded short interfering nucleic acid molecules directed to HBV RNA, wherein the molecules comprise a sense and an antisense strand, wherein each strand is about 18 to about 27 nucleotides in length. Application '841 recites 2'-deoxy, 2'-deoxy-2'-fluoro, and 2'-O-methyl modifications at varying amounts in one or both strands, as well as terminal cap moieties including inverted deoxy abasic moieties. Application '841 recites a composition comprising the nucleic

acid molecule in a pharmaceutically acceptable carrier or diluent. Therefore, the instant claims are obvious in view of the claims of application '841.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Furthermore, the following serial numbers of co-pending applications contain claims in which an obviousness-type double patenting rejection would be applied:

10/664,668
10/576,690
11/265,730
10/576,751
11/684,465
11/369,108
10/567,888
10/923,536
11/499,633
11/499,529
11/499,520
11/499,533
11/502,893
10/562,561
10/825,485
11/255,139
10/921,554

It is Applicants' burden to file appropriate terminal disclaimers for all relevant applications listed above. Furthermore, if Applicants are aware of any pending applications or patents, which are not listed above, it is Applicants' duty to disclose these applications or patents, and to submit an appropriate terminal disclaimer over these applications or patents as pertinent to the instant invention.

It is noted that the instant claims are considered obvious in view of any other claim set that recites chemically modified double stranded nucleic acid molecules targeting any RNA sequence, wherein the sense and antisense strand are within the same size range and have the same types of chemical modifications and terminal cap moieties, since the instant claims are not directed to any specific target sequence.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755. The examiner can normally be reached on Monday-Thursday 6:30 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amy H. Bowman/
Patent Examiner
Art Unit 1635